REMARKS

Claims 1, 2 and 4 to 6, 8 to 13 and 15 to 25 are pending in the present application. Claims 3, 7, and 14 are cancelled. Claims 1, 2, 15 to 22 are withdrawn. Claim 1 has been amended. Support for this amendment can be found in, e.g., paragraph [0021] and paragraph [0016] of the publication of the application (US application **20070048363)**.

WITHDRAWAL OF FINALITY OF THE OFFICE ACTION

The Office issued a final Office Action. A request to withdraw the finality of the Office Action was submitted on December 16, 2009 and considered. The finality of the Office Action was not withdrawn. Instead, the basis for applicant's argument, namely the new species election was removed. However, applicant notes that in the 35 U.S.C. 112, SECOND PARAGRAPH, REJECTION, discussed herein, is a new rejection also not caused by any action of applicant and, while not equally significant as the new election request, is still is a valid basis to request reconsideration the finality of the Office Action.

ELECTION/RESTRICTION

Species

Applicant would like to thank the Office for withdrawing the request to elect a specie per advisory action of January 12, 2010 in view of applicant's submission of December 16, 2010.

Kit claims

With respect to the newly added kit claims the Office stated that

"*claims 24 and 25 are independent and distinct from the invention originally claimed for the flowing reasons:*

Claims directed to a kit was withdrawn from consideration in the Office Action dated 10/29/08, in view of an election without traverse filed 6/19/08." (*emphasis added*)

Applicants would like to point out:

(a) that in a national stage application, the Office should consider whether the common technical feature of the claims is special, not whether claims are "independent and

distinct" from the remainder;

(b) that the election of 6/19/08 was made with traverse.
The Office had argued that the common technical feature of groups I and group II, as identified in the Restriction Requirement of May 19, 2008, was not special as it was not novel. The common technical feature was identified as being cis-diammoniumdichloro-trans-dihydroxyplatinum (IV). Applicant's traverse consisted of an amendment to claim 4 to incorporate all limitations of kit claim 1 (that previously only referred to "components" of claim 1) and an argument that this amendment rendered the restriction moot.

(c) The Office responded citing form paragraph 8.25.02 of MPEP 818.13(c) stating that *applicant did not distinctly and specifically point out the supposed errors in the restriction requirement,* and that *thus the election has been treated as an election without traverse.*

Applicant notes that form paragraph 8.25.02 refers to MPEP §818.03(a), which clarifies that a traversal is subject to the same rules as any reply by applicant under 37 CFR §1.111. Distinctly and specifically pointing out the supposed errors in the Office's action it is one way of rebutting a rejection. However, another frequently employed way is amending the claim(s) and arguing that the amendment removed the basis for the rejection. This second way constitutes a complete reply to an Office Action under 37 CFR §1.111 as much as the first way and is exactly what happened in the instant case.

(d) In view of the fact that the Office had not reconsidered applicants traversal argument under 37 CFR §1.111 in compliance with 37 CFR §1.112, applicant found another way to emphasize that the common technical feature of the claims grouped in group I and II was special by adding claims 24 and 25.

Applicant notes that amended claim 4 was, despite two Office Actions on the merits, never rejected under 35 USC 102 in view of Presnov (1988) which the Office had cited to support the statement that the common technical feature of the group I and II claims were not special. This supports that the amendment to claim 4 did in fact accomplish applicant's goal, namely to provide a common technical feature that was special.

In view of the above, applicant respectfully requests that Office either

(i) answers applicant's traversal in compliance with 37 CFR §1.112, or

(ii) considers whether or not the common technical feature of new claims 24 and 25 is special relative to the pharmaceutical composition claims.

35 U.S.C. 112, SECOND PARAGRAPH, REJECTION

On page 3, the Office rejected claims 4 to 6, 8 to 13 and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office noted that claim 4 recited the limitation "a gel" in line 22, but that there is insufficient antecedent basis for this recitation in the claim.

Applicant has amended the claims to provide such an antecedent basis.

Applicant also notes that this is another new rejection in a final Office Action not caused by an amendment by applicant and provides a further and separate basis for a request to withdraw the finality of the Action of October 1, 2009, which is hereby submitted for the Office's consideration.

35 U.S.C. §103(a) REJECTION

On page 4, the Office rejected claim 4 under 35 U.S.C. 103(a) as being unpatentable over Presnov et al. (hereinafter "Presnov") in view of US patent 4,658,048 to Totani et al (hereinafter "Totani').

The Office expressed the opinion that Presnov teaches cis-diammoniumdichloro-dihydroxoplatinum(IV) (which the Office refers to as "cis-oxoplatin") in a solution for infusion/injection where the solution comprises in addition to this "cis-oxoplatin" an aqueous saline solution and is administered intraperitoneally. The Office referred to page 74 of the Presnov. The Office further referred to Table 1 of Presnov for a specific example of 15-25 mg/kg, Table 3 for a specific example of 80mg/kg and Table 4 for a specific example of 10-90mg/kg.

The Office acknowledged that Presnov does not explicitly teach a low toxic carrier system.

However, the Office expressed the opinion that Totani teaches a low toxic injection solution comprising 5% aqueous mannitol suitable for the delivery of platinum (IV) compounds (abstract; col. 5, lines 1-5).

The Office concluded that it would have been obvious to one of ordinary skill in the art to optimize the injection solution of Presnov in view of Totani to arrive at the present invention.

Applicant respectfully submits that Presnov discloses teaches cis-diammoniumdichloro-dihydroxoplatinum(IV) ("oxoplatinum") in combination with saline.
Presnov reports that his oxoplatinum is 10 times less toxic than the platinum (II) compound DDP and otherwise also compares favorably to DDP. On page 82 Presnov also refers to a study by Tobe and Khokhar. In this study different tetravalent platinum complexes were tested. Tobe and Khokhar in particular discuss yet another tetravalent platinum complex that was promising, namely CHIP (cis-dichlorobis(isopylamine)-trans-dihydroxoplatinum(IV)).

Totani does not disclose cis-oxoplatin, but a number of platinum (IV) complexes that have lower nephrotoxicity than cisplatin.
Totani describes efforts to find analogous to cisplatin which was initially shown to have antitumor activity, but suffers from high toxicity. The authors note that many platinum complexes, among others, cis-dichloro-transdihydroxy-bis(isopropylamine)platinum(IV) [U.S. Pat. No. 4,394,319] are known. Totani, in an further effort, prepared novel platinum(IV) complexes which have a bidentate ligand.

Thus, Presnov and Totani both make clear that different platinum complexes including platinum (IV) complexes cannot be readily considered to have exchangeable properties.

In view of the varying properties of the platinum complexes, including (platinum (IV)) complexes, applicant submits that the person skilled in the art would not expect that a combination of different platinum complexes with other substances provide similar results.

More significantly, it is also clear that Totani considers his observed lower nephrotoxicity relative to cisplatin a function of their compound, not of any combination with a base material and thus provides little incentive to a person skilled in the art to even try to test such combinations to reduce the toxicity. In particular, Totani states:

> "The compounds of the present invention . . .have antitumor activity comparable to or more potent than that of cisplatin with lower nephrotoxicity. Furthermore, they can easily be administered parenterally since they are highly soluble in water. Thus, for example, the compounds (I) may be dissolved or suspended in appropriate solvents for injection (e.g., distilled water for injection, physiological saline, 5% aqueous glucose, 5% aqueous mannitol, aqueous ethanol, aqueous glycerin, and aqueous propylene glycol), and can be administered intravenously, intramuscularly, or subcutaneously, or by means of instillation." (paragraph bridging col. 4 and 5; *emphasis added*)

Thus, Totani does not disclose cis-oxoplatin, but a number of platinum (IV) complexes that have lower nephrotoxicity than cisplatin. These platinum (IV) complexes may be solubilized, e.g., in 5% aqueous mannitol. However, aqueous mannitol was clearly only recognized as a solvent and not as "result-effective" variable in accordance with MPEP §2144.05, II, B.
MPEP §2144.05, II, B makes clear that a optimization of ranges is only possible when a particular parameter is "recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." citing *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

The present invention is directed at a pharmaceutical agent comprising

(1) *cis*-diammoniumdichloro-*trans*-dihydroxoplatinum(IV) (*cis*-oxoplatin) and/or salts thereof, and (2) a base material resulting in specific compositions, in particular:

cis- oxoplatin : silicon dioxide : mannitol or magnesium stearate at a ratio of 0.1 to 10 : 0.1 to 10 : 0.1 to 10 (**for capsules**);

cis-oxoplatin : lactose : corn starch : poly(O-carboxymethyl)starch sodium salt : calcium hydrogen phosphate $\times$ $2H_2O$: cellulose powder : magnesium stearate at a ratio of 10 to 500 : 20 to 150 : 1 to 10 : 1 to 10 : 1 to 10 : 1 to 10 : 0.1 to 7; **or**
cis-oxoplatin : silicon dioxide : magnesium stearate at a ratio of 0.1 to 10 : 0.1 to 10 : 0.1 to 10 (**for**

tablets);

cis-oxoplatin : benzyl alcohol : cetyl stearyl alcohol : Macrogol stearate 1000 : isopropyl palmitate : glycerol : 70% sorbitol solution : water at a ratio of 0.2 to 8 : 0.1 to 7 : 1 to 10 : 0.1 to 7 : 0.1 to 7 : 0.2 to 8 : 0.2 to 8 : 20 to 60 (**for creams**);

cis-oxoplatin : propylene glycol : Macrogol stearate 1000 : cetyl stearyl alcohol: petrolatum at a ratio of 2 to 20 : 5 to 40 : 0.1 to 7 : 1 to 10 : 25 to 400 (**for ointments**);

cis-oxoplatin : hydroxyethylcellulose : chloroaerosol : sodium hydroxide : sodium hydrogen phosphate dihydrate : water at a ratio of 2 to 20 : 100 to 600 : 5 to 40 : 0.1 to 7 : 20 to 60 : 3,000 to 50,000 (**for gels**);

cis-oxoplatin : silicon dioxide : hardened fat at a ratio of 0.1 to 10 : 0.1 to 10 : 30 to 300; **or**
cis-oxoplatin : lactose : corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : highly dispersed silicon dioxide : Polysorbate 80 at a ratio of 10 to 100 : 700 to 4,000 : 200 to 600 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 10; **or**
cis-oxoplatin : lactose $\times$ $1H_2O$: corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : silicon dioxide : Polysorbate 80 at a ratio of 10 to 100 : 1,000 to 5,000 : 300 to 1,000 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 7; **or**
cis-oxoplatin : lactose $\times$ $1H_2O$: corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : silicon dioxide : Polysorbate 80 at a ratio of 10 to 1,000 : 1,500 to 5,000 : 300 to 1,000 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 7 (**for suppositories**);

cis-oxoplatin : benzyl alcohol : Polysorbate 80 : 70% sorbitol solution : water at a ratio of 0.2 to 8 : 1 to 10 : 0.1 to 7 : 100 to 800 : 100 to 400; **or**
cis-oxoplatin : mannitol : water at a ratio of 0.1 to 7 : 5 to 40 : 1 to 10 (**for solution for injection or infusion**).

The invention is based on the inventor's observation that an inclusion of cis-oxoplatin into a base material was observed to generally lead to a chemical transformation resulting not only in many adducts (hazardous products high in side effects) which already starts during the production process, but also prevents subsequent biotransformation in the body. The inventor addressed

this observed deficiency by providing specific pharmaceutical agents set forth in the claims.

The invention is also particularly well realized in a kit (see, e.g., paragraph [0010], [0014] to [0016] of the publication) that is combined to produce the pharmaceutical agent.

Thus, applicant discovered a pharmaceutical agent that allows the effective use of cis-oxoplatin which is combined with a base material so that the resulting pharmaceutical agent has substantially no toxic side effects as well as a kit to produce such a pharmaceutical agent.

The specific combinations of the pharmaceutical agents and kits are not taught by the combination of Presnov and Totani and go well beyond the results of routine experimentation that could be extrapolated from a combination of Presnov and Totani. The Office is again directed to the MPEP §2144.05, II, B, which lays out when such extrapolations would fall in the category of routine experimentation. Applicants submit that the conditions for such a extrapolation are not met in the present case.

Applicant also note that even if the prior art would have provided any hint of the fact that specific combinations which base material would be required, what applicants deny, the person skilled in the art was certainly faced with more than "a finite number of identified, predictable solutions, with a reasonable expectation of success," i.e., in the present case, type and concentrations of base materials (see MPEP §2141 (discussion of "obvious to try" rationale)).

Accordingly, applicant respectfully submits that no *prima face* case of obviousness of the invention as presently claimed has been established.

The fees required with this response are submitted herewith. However, the Office is authorized to charge undersigned's deposit account 50-3135 as required.

Respectfully submitted,

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